Characteristics of vascular involvement in Behçet's disease in Japan: a retrospective cohort study

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ABSTRACT

Objective. *We analysed the clinical vascular characteristics of Behçet's disease (BD) patients in Japan.*

Methods. *We retrospectively reviewed the clinical charts of 412 patients who fulfilled the 1987 Japanese criteria for BD and were treated in two University hospitals from July 1991 to December 2007. Patients with superficial thrombophlebitis were excluded, since it is categorised as a skin manifestation according to the Japanese criteria.*

Results. *Twenty-six patients (6%) had large-vessel involvement. Mean ages at BD diagnosis and onset of vascular episodes were 39.7 and 41.6 years, respectively. Males predominated (62%). Arterial and venous lesions were found in 8 (31%) and 21 patients (81%), respectively, including 3 (12%) with both types. Pulmonary artery occlusion was the most common arterial lesion (n=5, 19%), followed by ascending aortic aneurysm (n=2, 8%). Limb deep vein thrombosis was the leading venous lesion (n=20, 77%). Cardiac complications (angina pectoris/aortic regurgitation) occurred in two patients. Gastrointestinal involvement was more frequent than in patients without vascular involvement ($p<0.001$); ocular involvement was less frequent ($p<0.05$). Only 3 patients (12%) required surgery. Patients received prednisone and immunosuppressants, including infliximab, for vascular and/or concurrent gastrointestinal involvement. Nine patients received warfarin, without bleeding complications. One patient died during the observation period, 4 days after surgery for an aortic aneurysm.*

Conclusion. *Frequency of vascular involvement in BD in Japan is lower than in other ethnic populations. Although one patient died during the observation, there was no fatal haemoptysis, even in patients receiving warfarin.*

Introduction

Behçet's disease (BD) is a multisystem disease characterised by recurrent oral and genital ulcers, relapsing uveitis, and mucocutaneous, articular, urogenital, intestinal, neurologic, and vascular manifestations. The diagnosis of BD is based on a combination of clinical manifestations because there are no definitive diagnostic biomarkers.

The Chapel Hill consensus conference on the classification of vasculitis recognised BD as a type of vasculitis. However, whereas other vasculitis syndromes affect mainly the arterial system, BD-associated lesions are distributed in both the arterial and venous systems, including the pulmonary circulation system, irrespective of the size of the vessels (1). Previous studies among different ethnic groups have found that the prevalence of vascular involvement varies from 6.7% to 51.6% (2-14). Venous involvement is generally more common than arterial (88% *vs.* 12%) (3). On the other hand, arterial involvement such as aneurysms and arterial thrombosis occur in 1% to 34% of patients (12, 14) and can be lethal. These data suggest that there may be differences among ethnic populations in the prevalence and clinical features of vascular involvement in BD patients.

A recent study demonstrated that arterial involvement is one of the factors associated with mortality in BD (15). It is difficult to apply the clinical management used in other diseases, because vascular involvement is unique and serious in BD. Indeed, there is no established evidence to guide the management of major vessel disease in BD (16), although corticosteroid and immunosuppressants such as azathioprine (17), cyclophosphamide, or cyclosporine A (18) are recommended for pulmonary (19) and peripheral arterial aneurisms and acute deep vein thrombosis in BD. On the other hand, anti-

thrombotic therapies for arterial and venous lesions are controversial because of the increasing risk of rupture of concurrent pulmonary artery aneurysms. It is important to characterise the clinical features and determine whether, and how, they differ among ethnic groups to optimise the strategy for managing vascular involvement in BD.

This study retrospectively examined the clinical features, treatment, and outcomes in 26 BD patients with vascular involvement out of a total 412 BD patients who were treated at two university hospital departments during a 16.5-year observation period. We also compared these data with those from previous reports on different ethnic populations.

Table I. Comparison of clinical features in Behçet's disease patients.

	With vascular involvement (n=26)	Without vascular involvement (n=386)	All (n=412)	*p*
Age at disease onset (years)*	39.7 ± 13.5 (38.8, 28.1 to 49.8)	36.7 ± 11.8 (35.6, 27.8 to 43.7)	36.9 ± 11.9 (35.8, 27.8 to 44.2)	NS
Male sex	16 (62%)	168 (44%)	184 (45%)	NS
Interval between symptom onset and diagnosis of BD (years)*	7.8 ± 9.4 (5.1, 1.8 to 9.9)	8.6 ± 10.2 (4.2, 0.7 to 13.3)	8.6 ± 10.1 (4.5, 0.8 to 13.1)	NS
Follow-up duration (years)*	5.9 ± 6.3 (3.3, 1.6 to 7.9)	7.3 ± 6.8 (5.2, 1.5 to 12.5)	7.2 ± 6.7 (5.2, 1.5 to 12.5)	NS
HLA-B51 positivity	6/15 (40%)	118/233 (51%)	124/248 (50%)	NS
Oral ulcers	26 (100%)	374 (100%)	410 (100%)	NS
Genital ulcers	16 (62%)	283 (73%)	299 (73%)	NS
Eye involvement	11 (42%)	255 (66%)	266 (65%)	0.014
Skin involvement	24 (92%)	339 (88%)	363 (88%)	NS
Arthritis	14 (54%)	184 (48%)	198 (48%)	NS
Epididymitis	1/16 (6%)	10/168 (6%)	11/184 (6%)	NS
Gastrointestinal involvement	8 (31%)	35 (9%)	43 (10%)	0.000
Central nervous system involvement	2 (8%)	52 (14%)	54 (13%)	NS
Pathergy test positivity	4/8 (50%)	50/112 (45%)	54/120 (45%)	NS
Complete type	6 (23%)	137 (36%)	143 (35%)	NS

*Data are presented as means ± SD (median, interquartile range).

Methods

The study included all patients who met the 1987 (20) or 2003 (21) revised Japanese criteria for the diagnosis of BD and were treated in the two Yokohama City University Hospitals, located in central Japan, in the period July 1991 to December 2007. The Japanese criteria list recurrent aphthous ulcers of the oral mucosa, skin lesions (such as erythema nodosum, acne, or cutaneous hypersensitivity), ocular inflammation, and genital ulcers as the major symptoms of BD. Arthritis, intestinal ulcers, epididymitis, vascular lesions (such as obliteration, occlusion, and aneurysm), and neuropsychiatric disease are included as minor symptoms. Superficial thrombophlebitis is the most frequent type of vascular lesion. However, it is categorised as skin involvement in accordance with the Japanese criteria. Patients with 4 major symptoms during the clinical course were defined as having complete-type BD. Patients with 3 major symptoms, with 2 major and 2 minor symptoms, with typical recurrent ocular inflammation and 1 or more major symptoms, or with typical recurrent ocular inflammation and 2 minor symptoms were defined as having incomplete-type BD. Those patients with one or two major symptoms who did not satisfy the requirements for the incomplete type were defined as having suspected BD. We included patients with complete or incomplete BD in this investigation, but we excluded those with suspected BD because we intended to investigate only patients with a definitive diagnosis. Moreover, patients who had gastrointestinal, large vascular, or central nervous system involvement were categorised as having special disease types, defined as intestinal, vasculo-, or neuro-BD, respectively.

Diagnosis of vascular lesions was based on clinical assessments and imaging techniques, including angiography, venography, CT scan, MRA, ultrasonography, pulmonary perfusion, and single photon emission computed tomography (SPECT).

We compared the sex, age at onset of each BD symptom, age at BD diagnosis, HLA phenotype, and follow-up period in 412 selected patients. All patients underwent a detailed medical interview and routine physical examinations, and the findings were documented by specialists qualified in each field, including ophthalmologists, rheumatologists, dermatologists, neurologists, and gastroenterologists. The medical files were reviewed for clinical findings at regular follow-up examinations. Data on demographic parameters and laboratory results were recorded as well.

Twenty-six of the 412 patients had vascular involvement. Superficial thrombophlebitis was excluded, because it is considered a skin manifestation in accordance with the Japanese Criteria.

Statistical analysis was performed with the SPSS version 11.0 software package (SPSS Inc., Chicago, Illinois, USA). The categorical variables were analysed by using the chi-squared test or Fisher's exact probability test. Continuous variables were analysed with Student's *t*-test or Welch's *t*-test, as appropriate. A value of $p<0.05$ was considered statistically significant.

Results

The study included 184 male and 228 female BD patients who were treated at one or more care units at two university hospitals over a period of 16.5 years. All but three patients were Japanese (one Chinese, one Korean, and one Syrian). Twenty-six of the patients (6.3%), who were all Japanese, were classified as having vasculo-BD (Tables I, II). The mean observation period was 5.9±6.3 years (median 3.3, interquartile range 1.6 to 7.9 years). Although vascular involvement developed at an average of 2.2±8.4 years (median 0.0, interquartile range -3.3 to 4.5 years) after the diagnosis of BD was established (22), five patients had vascular lesions

Table II. Frequencies of vascular involvement in previous reports.

	Reference	Country	Year	Total no. of BD patients	Total no. of vasculo-BD patients	Arterial involvement	Venous involvement
Clinical study							
	(2)	Japan	1972	2031	142 (7%)	–	–
	(2)	Japan	1991	3316	298 (9%)	–	–
Koç Y, *et al*.	(3)	Turkey	1992	137	27 (19.7%)*	5 (4%)	22 (16%)
Kabbaj N, *et al*.	(4)	Morocco	1993	125	40 (32%)*	6 (5%)	36 (29%)
Graña Gil J, *et al*.	(5)	Spain	1993	23	2 (8.7%)	1 (4%)	1 (4%)
al-Dalaan AN, *et al*.	(6)	Saudi Arabia	1994	119	37 (31.1%)*	22 (18%)	30 (25%)
Gürler A, *et al*.	(7)	Turkey	1997	2147	222 (10.3%)*	25 (1%)	197 (9%)
Ko GY, *et al*.	(8)	Korea	2000	64	33 (51.6%)*	21 (33%)	22 (34%)
Kural-Seyahi E, *et al*.	(9)	Turkey	2003	387	88 (22.7%)*	21 (5%)	82 (21%)
Tohmé A, *et al*.	(10)	Lebanon	2003	140	18 (13%)*	6 (4%)	17 (12%)
Düzgün N, *et al*.	(11)	Turkey	2006	180	71 (39.4%)*	20 (11%)	68 (38%)
Sarica-Kucukoglu R, *et al*.	(12)	Turkey	2006	2319	155 (6.7%)	24 (1%)	140 (6%)
Kikuchi H, *et al*.	(13)	Japan	2010	277	42 (15.2%)*	12 (4%)	34 (12%)
Present study	(22)	Japan		412	26 (6.3%)	8 (2%)	21 (5%)
Autopsy study							
Lakhanpal S, *et al*.	(14)	Japan	1985	170	74 (43.5%)*	57 (34%)	17 (10%)

*Significantly higher frequency compared with the present study ($p<0.05$).

as initial signs. The five patients were diagnosed with BD because of the vascular involvement, which is listed as a minor symptom in the Japanese criteria. The frequency of vascular involvement was lower than that in any previous studies of various ethnic groups; these studies found that 6.7% to 51.6% of BD patients developed vascular lesions (Table II). However, our value was not significantly different from 3 of 4 previous large scale studies which enrolled more than 2,000 patients (2, 7, 12) (Table II). When the International Study Group (ISG) criteria (23) was applied to this study, the frequency of vascular involvement was 5.1% (19/370 patients).

We compared the clinical features and backgrounds of vasculo-BD patients with those of BD patients with no vascular lesions (Table I). Vasculo-BD was male-predominant (62%), whereas females predominated in the other BD subtypes (female 56%). There were no significant differences in age of onset or disease duration. There was also no difference in the frequency of HLA-B51 positive patients, although HLA status was not determined in all patients.

We found three significant features among the extravascular clinical manifestations. First, eye involvement was significantly less frequent among patients with vasculo-BD. This resulted in a lower incidence of the complete type of vasculo-BD: 6 of 26 vasculo-BD patients (23%) were classified as having the complete type, whereas 143 of all 412 BD patients (35%) were included

Table III. Anatomical distribution of vascular lesions in vasculo-BD patients.

a) Arterial system

Arterial lesions	No. of patients	No. of arteries involved
Pulmonary artery occlusion	5	7
Ascending aortic aneurysm	2	2
Arterial thrombosis in limb	1	1
Total	8	10
Interval between BD onset and emergence of arterial involvement		
Mean ± SD (range)	6.2 ± 10.2 (–7.0 to 21.6)	
Median	1.9	
Interquartile range	–0.2 to 17.5	

b) Venous system

Venous lesions	Patients	Number of veins involved
Deep vein thrombosis in limb	20*	26
Femoral vein thrombosis		6
Popliteal vein thrombosis		3
Iliac vein thrombosis		1
Undetermined		16
Central retinal vein thrombosis	1	1
Sagittal and transverse sinus thrombosis	1*	2
Total	21	29
Interval between BD onset and emergence of venous involvement		
Mean ± SD (range)	1.3 ± 7.8 (–10.1 to 19.5)	
Median	0.3	
Interquartile range	–3.5 to 1.2	

*One patient had sagittal and transverse sinus thrombosis, and popliteal vein thrombosis simultaneously.

in that category. Five of 11 patients having both eye and vascular involvement presented vascular lesions followed by eye symptoms. Only 6 of 261 (2.3%) patients who had pre-existing eye involvement developed vascular lesions later. Second, vasculo-BD patients had significantly more frequent gastrointestinal involvement than the other subtypes. Finally, positive pathergy tests were more common in male than in female patients with vasculo-BD patients (male 80% *vs*. female 0%, p=0.028), although pathergy was tested in only 8 of the 26 patients. In contrast, the rate of positivity of pathergy testing was comparable between male and female patients without vasculo-BD (male 47% *vs*. female 44%).

We next examined the anatomical localisation and pathology of vascular lesions (Table III). Whereas 8 patients (31%) had 10 arterial lesions, 29 venous lesions were found in 21 patients (81%). Three patients had multiple lesions distributed in both the arterial and venous systems.

The most frequent type of arterial involvement was pulmonary arterial occlusion, which was found in 7 arteries in 5 patients (Table IIIa). However, no patients had haemoptysis. Two patients had an ascending aortic aneurysm and one had limb artery thrombosis.

Deep vein thrombosis was the most frequent type of venous lesion (20 patients, 26 veins). Areas where these lesions were distributed included 6 femoral veins, 3 popliteal veins, and 1 iliac vein (Table IIIb). Six patients had venous thrombosis in both lower limbs. Central retinal vein thrombosis and sagittal and transverse sinus thrombosis were found in one patient each. Although vascular lesions are generally recognised as late-onset manifestations of BD (22), some patients developed vascular lesions early in their clinical courses, before they satisfied the diagnostic criteria for BD. Venous lesions appeared earlier than arterial lesions, although the difference was not statistically significant. The interval between BD onset and emergence of vascular involvement was 1.3±7.8 years (median 0.3, interquartile range -3.5 to 1.2 years) in patients with venous lesions and 6.2±10.2 years (median 1.9, interquartile range -0.2 to 17.5 years) in those with arterial lesions (p=0.181) (Table III). No significant difference was found between two groups.

Two patients presented with cardiac involvement (2 of 26, 8%). Angina pectoris complicated by deep vein thrombosis in the limb was found in a male patient, and a female patient developed a pseudoaneurysm of the ascending aorta, with aortic regurgitation.

We categorised the vasculo-BD patients into those with arterial lesions and those with venous lesions and compared the incidence of extravascular clinical manifestations between the two groups (data not shown). There was no difference in the frequency of eye involvement between the two groups, whereas gastrointestinal involvement was more common in patients with arterial lesions (75%; p=0.001). The pathergy test was negative in all 3 patients with arterial involvement that were tested, but the test was positive for 4 of 5 patients without arterial involvement, indicating a significant difference between the two groups (p=0.028).

We next divided the treatment strategies into three major categories: immunosuppressant and anti-inflammatory agents, anti-thrombotic agents, and surgical treatment (Table IV). Prednisone and immunosuppressants (cyclosporine, cyclophosphamide, azathioprine, mercaptopurine) were given to 14 (54%) and 7 patients (27%), respectively. Azathioprine, mercaptopurine, and infliximab were administered for concurrent gastrointestinal involvement. Although colchicine was the agent most frequently used (14 patients), the primary targets were mucocutaneous lesions.

Warfarin and aspirin were prescribed in 9 patients each. No patient had a serious bleeding episode, including haemoptysis.

Only 3 patients (12%) required surgery (Table IV). None of those patients required reoperation. The first patient (28-year-old female) had the left 1st and 2nd toes amputated when gangrene appeared as a result of arterial occlusion. The second patient (46-year-old male) underwent stripping surgery for leg varices caused by deep vein thrombosis. A 50-year-old female with a 23-year history of BD died from a pseudoaneurysm of the ascending aorta 4 days after surgical artificial aortic root replacement for aortic regurgitation. No other patient died during the observation period.

Two of 26 BD patients (7.7%) had relapses of vascular events during the observation period. Both were male. In spite of oral glucocorticoids, warfarin, and colchicine with or without immunosuppressants (cyclosporine, cyclophosphamide), as well as aspirin, they

Table IV. Surgical and pharmacological therapies in vasculo-Behçet's disease patients.

	With vascular involvement (n=26)	With arterial involvement (n=8)	Without arterial involvement (n=18)	p-value
Surgery	3	2	1	NS
Steroid pulse	2	1	1	NS
Oral glucocorticoid	14	5	9	NS
Immunosuppressants*	7	2	5	NS
Cyclosporine	6	1	5	NS
Cyclophosphamide	2	0	2	NS
Azathioprine	2	2	0	0.027
Mercaptopurine	1	1	0	NS
Infliximab	2	2	0	0.027
Colchicine	14	4	10	NS
Warfarin potassium	9	4	5	NS
Aspirin	9	1	8	NS

*Immunosuppressants including cyclosporine, cyclophosphamide, azathioprine, and mercaptopurine were given to 7 patients. Four of them received 2 agents of the immunosuppressants during the clinical courses.

repeatedly developed deep vein thrombosis in the limbs.

Although vascular involvement is thought to be associated with a poor prognosis, only 1 of the 26 patients died from vascular involvement during the observation period (mean 5.9±6.3, median 3.3, interquartile range 1.6 to 7.9 years).

Discussion

We found vascular involvement in 26 (6%) of the 412 BD patients. The frequency of vascular involvement was significantly lower than that in most previous studies but comparable to that in two previous large-scale epidemiological studies using the same inclusion criteria as used in Japan (2). The previous studies were based on simple questionnaires and did not include the details of the vascular manifestations in individual patients. In contrast, we reviewed the full spectrum of disease manifestations and had the largest cohort of vasculo-BD patients of this ethnic background. Major conclusions were unaltered if the ISG criteria were applied to the patients in this study. Kikuchi *et al*. found vascular involvement in 42 of 277 BD patients (15.2%) during a 20-year follow-up in Japan (13). This is consistent with our findings and suggests that the frequency of vascular involvement in BD in Japan is comparatively lower than in those of other ethnic groups.

Besides vasculo-BD, ethnical differences are found in other vascular diseases such as idiopathic venous thromboembolism (VTE). Idiopathic VTE is significantly less frequent in both Hispanics and Asians/Pacific Islanders ($p<0.001$) than in Caucasians or African-Americans. The incidence is 104 per 100,000 in Caucasians, 141 per 100,000 in African-Americans, 55 per 100,000 in Hispanics, and 21 per 100,000 in Asians and Pacific Islanders (24). Certain thrombophilic genetic predispositions, such as a factor V Leiden mutation (25, 26) and the prothrombin gene mutation (27), are rarely found in Asian populations (28, 29, 30, 31), although the contributions of these genetic factors to thrombogenesis in BD are controversial (32, 33). Elevated Factor VIII levels, resistance to activated protein C, and obesity are potential risk factors for VTE, and these conditions are also rare, or of lower incidence, among Asians than in the Caucasian, African-American, and Hispanic populations (34, 35).

Recent studies have suggested that ethnicity is a predisposing factor to even secondary VTE. For example, deep vein thrombosis, but not arterial disease, is less common in systemic lupus erythematosus (SLE) in Asian-American and Chinese populations than in others (36, 37). In addition to being associated with disease-related factors such as the prevalence of antiphospholipid and antiprothrombin antibodies (37, 38), the incidence of VTE in SLE patients is modulated by the prevalence of acquired activated protein C resistance (39), thrombogenetic predisposition (including factor V Leiden mutation) (40, 41), β2-glycoprotein I genetic mutation (42), and lifestyle habits, none which is directly associated with SLE.

In addition to the frequency of vascular involvement, the proportion of the venous and arterial lesions differs among the studies. Our results showed that veins were affected more frequently than arteries, consistent with previous studies from Turkey (3, 7, 11, 12), Morocco (4), Saudi Arabia (6), Lebanon (10), and Japan (13), whereas studies in Spain (5), and Korea (8) have reported that arterial lesions are as common as venous lesions. Moreover, an autopsy study from Japan showed a predominance of arterial lesions (14).

Determination of vascular involvement in individual studies is of critical importance. We diagnosed vascular involvement on the basis of clinical manifestations; most of the lesions were identified by imaging techniques, including angiography, venography, CT scan, MRA, ultrasonography, pulmonary perfusion, and SPECT, which were conducted on the basis of the judgment of the attending physicians. Table II shows that the highest frequency of vascular lesions among the previous reports was found in a Korean study (8) in which the diagnosis was made by CT or angiography. Moreover, postmortem pathological analysis (14) showed a much higher frequency of vascular involvement, especially in arterial lesions. The study of 170 BD patients autopsied from 1961 to 1976 revealed pathological vascular lesions in 43.5%, whereas four clinical studies showed that the incidence of vascular lesions ranged from 6.3% to 15.2% in the same population (2, 13, 22). These data suggest that BD patients have latent vascular lesions that are not noticed in daily clinical practice, and that the reported frequency of vascular lesions depends on the sensitivity of the detection techniques in individual studies.

The severity of the disease must be considered when comparing data from autopsied patients with those from clinical analyses. The majority of BD patients die from other diseases, because BD is associated with a limited number of lethal conditions (15). The pathological findings in a postmortem study that enrolled patients who died of BD were closely associated with BD-related causes of death (14). The fatal events may be a direct result of vascular involvement. Indeed, Saadoun *et al*. showed that the frequency of arterial involvement in patients who died of BD was 3 times that in surviving patients (15). Therefore, it is likely that a high frequency of arterial lesions is associated with disease severity and fatal events in autopsied patients. However, only one of the patients in our study died, from a pseudoaneurysm of the ascending aorta 4 days after surgical artificial aortic root replacement. Of course, the effects of treatment or the healing process, as well as the possibility of an incomplete postmortem examination, can affect reporting in postmortem analyses (14).

Vascular lesions developed 2.2±8.4 years (median 0.0, interquartile range -3.3 to 4.5 years) after diagnosis in the current series of patients (22). Only 5 of 26 patients presented with vascular involvement as the initial manifestation. It is helpful to determine the predisposing factors for the development of vascular involvement. As previously shown, we found that several extravascular clinical features were associated with the development of vascular involvement. These included male predominance (9, 11),

a lower frequency of eye involvement (11), and a higher frequency of gastrointestinal involvement in vasculo-BD patients (10). Interestingly, 75% of the patients with arterial involvement had simultaneous gastrointestinal lesions, suggesting that arterial involvement has specific pathological implications in gastrointestinal lesions. Although previous studies have shown that a positive pathergy test occurs more frequently in vasculo-BD than other subtype BD patients (3, 43), we found this to hold true in male, but not female, patients. The cause of these gender differences is uncertain, although some studies have demonstrated that a positive pathergy test is more commonly seen in males than in females, irrespective of the clinical subtype of BD (43, 44).

Our results revealed that eye involvement appeared significantly less frequently in vasculo-BD than BD patients without vascular involvement. Therapy for ocular lesions may help to suppress the development of vascular involvement, because azathioprine, for example, has long-term preventive effects against vascular lesions (14, 45). Vascular involvement is recognised as a late-onset manifestation (22). Nevertheless, in our retrospective study, vascular lesions were found in only 6 of 261 (2.3%) patients who had preceding ocular lesions. Immunosuppressants, including cyclosporine, tacrolimus, azathioprine, cyclophosphamide, and methotrexate, were used more commonly in patients with ocular lesions (36.1%) than in those without ocular lesions (10.3%).

Development of thrombosis is usually associated with increased serum levels of acute phase reactants, suggesting that inflammatory processes are involved in the thrombotic tendencies associated with BD (46, 47). Therefore, immunosuppressive drugs are the cornerstone of treatment in the case of thrombosis. Indeed, corticosteroids and immunosuppressants were the predominant pharmacological therapies in our patients. In contrast, the risks and benefits of anticoagulant therapy are controversial. A recent retrospective study did not show that additional anticoagulant therapy suppresses the recurrence of thrombosis in BD patients with venous thrombosis that are treated with immunosuppressants (47). However, several reports have shown that anticoagulant therapy increases the risk of fatal haemoptysis (48, 49). These findings indicate that anticoagulant therapy for thrombosis is unfavorable in BD patients. Recently, EULAR recommends that anticoagulation therapy should be avoided because of the low risk of pulmonary embolism and the high risk of fatal bleeding from a coexisting pulmonary arterial aneurysm in vasculo-BD patients. However, warfarin was commonly used among our vasculo-BD patients. Some of them were treated before the reports which alarmed increased risk of anticoagulant therapy-related fatal haemoptysis (48, 49). The frequency in Japan is uncertain, although sporadic cases of BD with pulmonary arterial aneurysm in Japanese patients have been described in English and Japanese reports (50-53). A postmortem study of BD patients in Japan recorded pulmonary arterial thrombosis and pulmonary arteritis in 5 (2.9%) and 1 (0.6%) respectively, although there were vascular lesions in any of the organ systems in 74 (43.5%) of 170 patients. Fortunately, our study showed no incidence of warfarin-related major adverse events. Similar observations have been reported in the UK (54): they showed that 62 of 657 BD patients (9%) had a history of thrombosis over 15 years. Seventeen of these were thought to have had pulmonary emboli, and most [55 patients (89%)] of the patients were being treated with warfarin at the time of thrombosis and before referral to the study center. Warfarin was discontinued in only two patients because of complications. Although the risk of anticoagulation therapy-associated bleeding events might differ among different ethnic groups, these observations, including those presented here, do not necessarily justify the use of warfarin. Physicians should be aware of the potential risks of anticoagulant therapy-related bleeding events in BD patients.

Cardiac involvement is thought to be uncommon in BD patients (55), although some studies have reported a relatively high frequency, ranging from 7% to 46% of patients (56). The pathological features vary and include endocarditis, myocarditis, pericarditis, acute myocardial infarction, aortic aneurysm, ventricular thrombosis, congestive cardiomyopathy, and valvular dysfunction (57, 58). There were only two patients in our study with potentially lethal manifestations; one of them died of pseudoaneurysm of the ascending aorta complicated with aortic regurgitation.

In conclusion, vascular involvement occurred less frequently as a clinical manifestation of BD in this study than in most of previous studies. It was associated with male gender, a high frequency of gastrointestinal involvement, and a low incidence of ocular lesions. Although there were serious lesions, such as pulmonary artery occlusion and aortic aneurysm, only one patient died during the observation period. Despite common use of warfarin, fatal haemoptysis from pulmonary lesions was not found in this study. These findings may be representative of the features of vasculo-BD patients in Japan.

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